Marked-Up Version of Claims

1. (Twice amended) A method of targeted delivery of mammalian stem cells of myeloid origin into a nervous system of a mammal by administering a therapeutically effective amount of mammalian stem cells of myeloid origin into said nervous system of said mammal, whereby

said mammalian stem cells of myeloid origin migrate from an injection site to a preferred site in said nervous system of said mammal, and

said mammalian stem cells of myeloid origin engraft into said nervous system of said mammal and differentiate into neuronal cells [at said preferred site].

5. CANCELED

6. CANCELED

7. CANCELED

14. CANCELED

15. CANCELED

18. CANCELED

19. CANCELED

REMARKS

Claims 1-19 are pending in the application. Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph, because the invention has not enabled one of skill in the art to make and use the invention for the entire scope claimed. Claims 1-9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Eglitis *et al.* (PNAS Vol. 94 1997).

Claim 1 has been amended. Claims 5-7, 14, 15, 18, and 19 have been cancelled without prejudice. While Applicants believe that the originally presented claims are patentable over all of the art of record and otherwise in view of all references submitted by Applicants, the claims have nonetheless been amended or canceled as follows in order to expedite the application toward allowance. The amendment and cancellations are therefore made without prejudice or disclaimer, and Applicants reserve the right to pursue the original scope of the claims as provided prior to the cancellation or amendments, such as through continuation practice. Support for the amendment to claim 1 can be found throughout the specification and in the claims as filed. For example, support for the phrase "differentiate into neuronal cells" can be found at page 7, lines 21-23; page 8, lines 4-6; and page 9, line 10. Accordingly, no new matter has been added by the proposed amendments.

Applicants respectfully traverse the Examiner's rejections and request reconsideration of the application in view of the amendments made above and the remarks that follow.

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 1-19 remain rejected under 35 U.S.C. § 112, first paragraph. In particular, the Office Action states that "the present invention while enabled for rats and mice is not enabled for all mammals, including humans." The Office Action further asserts that:

> [t]he fact that mouse and rat models are used in the art does not necessarily render the method claimed predictable such that one of skill in the art can make and use the invention without undue experimentation.

The Office Action further asserts that:

> The references cited by Applicant on page 11 of the response filed 23 August 2002 all relate to the use of either rat or mouse model. *None of which disclose the use of their methods with human subjects.* Moreover, none of these references disclose the grafting of stem cells or myeloid stem cells into a rat model...Therefore, these reference do not overcome the unpredictability in the art of stem cell replacement. (Emphasis added.)

While Applicants appreciate the Examiner's careful scrutiny of the references presented, Applicants respectfully disagree with the basis of this rejection in light of recent work in the field of stem cell research. Specifically, the work by Mezey *et al.* (*PNAS* (2003) 100 (3): 1364-1369) demonstrated, through the use of bone marrow transplants, which includes myeloid stem cells, that the methods of the present invention can be extended to humans as taught by the Applicants' specification.

The recent study by Mezey *et al.* (*PNAS* (2003) 100 (3): 1364-1369) describes the generation of new neurons in human brains following bone marrow transplants. All mature blood cells are believed to originate from very primitive cells in the bone marrow called pluripotent stem cells in the bone marrow. Pluripotent stem cells are capable of producing other stem cells, such as lymphoid stem cells and myeloid stem cells, from which the various types of mature blood cells evolve. In this recent study, female patients who had received bone marrow transplants from males were screened for Y chromosome-positive neuron-like cells in their brains. The results showed Y-chromosome positive cells in *both neurons and microglia*. Thus, the Mezey *et al.* study

confirms that the methods demonstrated in the Applicants' application in mice and rats are extended to humans.

Applicants' specification clearly describes cell migration following the injection of mammalian stem cells of myeloid origin into multiple target regions leading to differentiation into developmentally and regionally appropriate cells, such as neuronal and glial cells (*See* page 23, line 21-27). The results show that this modification occurs at particular desired regions, i.e. those that are damaged, and demonstrate that "cells show a natural ability to migrate away from the injection site, travelling preferentially to lesioned areas in all lesion models (i.e., lysolecithin, NMDA, 6-OHDA)" (*See* page 23, lines 29-31). In light of the study by Mezey *et al.*, there is no reason to believe that the Applicants' results in art-recognized models would not be replicated in other mammals.

Applicants submit concurrently herewith a Declaration of Dr. Matthew J. During pursuant to 37 C.F.R. §1.132 to overcome these rejections. This Declaration establishes that one skilled in the art would be able to use the application's disclosure to apply the invention to other mammals. Paragraph 7 clearly states that the rat and mouse models of CNS disorders used in the application are well-recognized in the art to correspond to disorders of other mammals. Hence, there is no reason to believe that the same results achieved in these well-recognized models would not be reproduced in other mammals. In fact, initial evidence indicating that the underlying principle of the invention is able to be reproduced in humans was recently shown by Mezey *et al.* (*Proc. Natl. Acad. Sci. USA* 100(3): 1364-1369 (2003)), as discussed above.

This Declaration obviates the rejection of claims 1-19 under 35 U.S.C. 112, first paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

The Examiner further contends that Bjorklund *et al.*:

> recognized that stem cell technology has to mature before human treatment is possible....[and]... 'believe that any clinical application of this new technology must await convincing preclinical data, no only to demonstrate efficacy by also to reveal the mechanism underlying any observed functional recovery.'

Furthermore, the Examiner states that:

> the transplanted cells must not trigger a host immune response, which would be detrimental to any gene transfer procedure

Applicants respectfully disagree with the basis for this argument. Applicants have shown that no systemic or local adverse response, or inflammatory response was induced using the methods of the present invention (See page 24, lines 3-8). In addition, the MPEP 2164.05(a) clearly states that proving efficacy and safety in clinical trials before the PTO is not required :

> considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney*, 34 F.3d 1058, 1063 32 USPQ2d 1115, 11120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")

Hence, proof of efficacy is not required for the application to be considered enabling.

Furthermore, the Examiner states that:

> Applicant's assertions and teachings in the specification fail to satisfy several issues regarding the state of and predictability of the art. Applicant *must show that the transgene contained in the stem cell* is stable and expresses over a long period of time in the subject...Applicant has not disclosed how long these cells will express the gene of interest or how they will survive. A significant obstacle to the development of gene therapy is the targeted long-term expression of the transgene, which is what Applicant purports its genetically modified myeloid stem cells can do....Gene therapy and stem cell therapy is unpredictable in nature such that it is difficult to extrapolate from animal models to human systems.

The Applicants disagree with the basis of this argument. However, in order to expedite prosecution, Applicants have cancelled claims 6, 7, 14, 15, 18, and 19. Since introduction of a transgene through the transfection of stem cells is claimed in claims 6, 7, 14, 15, 18, and 19, which are hereby cancelled, the

rejection based upon the gene therapy aspect of the claims is rendered moot. The Examiner is respectfully requested to withdraw this rejection.

For all the forgoing reasons, the Examiner is respectfully requested to withdraw the rejection of claims 1-19 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102(b)

Claims 1-9 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Eglitis *et al.* (PNAS Vol. 94 1997). In particular, the Office Action states that:

> [t]he invention of the instant claims is drawn to a method of delivery of mammalian myeloid derived stem cells into the mammalian nervous system of a mammal...[and] to the delivery of stem cells transfected with foreign genes...[including] administering stem cells into a subject mammal, the migrating of the cells into the nervous system and the engrafting of the cells in the brain. Eglitis et al. discloses the transplantation of myeloid cells marked with a retroviral vector into the brains of mice.. These cells are capable of migration to discrete parts of the brain and express the exogenous gene. Eglitis further discloses that myeloid derived cells acquire *microglial* antigenic markers and finds hematopoietically derived *microglia* in the brains of rats. (Emphasis added.)

Applicants respectfully traverse this rejection, as Eglitis *et al.* fails to teach each and every claim element of the claimed invention. The amendments submitted herewith further clarify the differences between the Eglitis reference and the present invention.

Eglitis *et al.* teaches that hematopoietic cells are capable of differentiating into *glial cells* after transplantation into brains of adult mice. Glial cells and neuronal cells are two different types of brain cells. Glial cells, which include astrocytes, oligodendrocytes, and microglia, function to provide structural support to neuronal cells, provide neurons with a protective myelin sheath, and remove dead cells and debris. As the Examiner indicated in the Office Action mailed August 29, 2001, Eglitis *does not teach* or suggest that hematopoietic stem cells are capable of differentiation into neuronal

cells. Claim 1, as amended, specifically recites that the engrafted mammalian stem cells of myeloid origin "differentiate into neuronal cells" whereas the teachings of the Eglitis reference do not provide any motivation or suggestion that hematopoietic cells can differentiate into neuronal cells. Furthermore, Eglitis *et al.* do not disclose selection of human myeloid stem cells, such as CD34+ cells. CD34 and kinase tyrosine receptor (KDR) are markers present on human stem as disclosed by the Applicants' specification (*See* page 12, lines 10-12 and lines 22-24). The absence of the claimed elements from the Eglitis reference negates anticipation. Accordingly, claim 1 and all claims dependent therefrom are not anticipated by the Eglitis reference. Applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. In the event that the amendments and remarks are not deemed to overcome the grounds for rejection, the Examiner is kindly requested to telephone the undersigned representative to discuss any remaining issues.

Respectfully submitted,

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